# Case Report Rapport de cas

## Protein-losing nephropathy associated with *Borrelia burgdorferi* seropositivity in a soft-coated wheaten terrier: Response to therapy

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**Abstract —** A soft-coated wheaten terrier was examined for lameness with subsequent identification of protein-losing nephropathy, hypoalbuminemia, hyperglobulinemia, and seroconversion to *Borrelia burgdorferi.* Following doxycycline therapy, the urine protein loss decreased significantly and serum albumin concentration remained close to or within the reference interval for over 3 years, contrary to the reported poor prognosis for renal disease associated with *B. burgdorferi* or protein-losing nephropathy of soft-coated wheaten terriers.

**Résumé — Néphropathie avec perte de protéines associée à une séropositivité pour *Borrelia burgdorferi* chez un Soft-Coated Wheaten Terrier : réponse au traitement.** Un Soft-Coated Wheaten Terrier (Terrier irlandais à poil doux) a été examiné pour boiterie avec l'identification subséquente d'une néphropathie avec perte de protéines, d'hypoalbuminémie, d'hyperglobulinémie et de séroconversion à *Borrelia burgdorferi.* Après un traitement à la doxycycline, la perte de protéines dans l'urine a affiché une baisse significative et la concentration sérique de protéines est demeurée conforme aux intervalles de référence pendant plus de 3 ans, contrairement au pronostic sombre signalé pour la maladie rénale associée à *B. burgdorferi* ou à la néphropathie avec perte de protéines des Soft-Coated Wheaten Terriers.

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Protein-losing nephropathy (PLN) is a condition of glomerular protein loss resulting from many different causes. Structural and functional alteration of glomeruli result in increased protein leakage across the filtration membrane and overt renal proteinuria. Soft-coated wheaten terriers (SCWT) have a familial predisposition to PLN which typically progresses to renal failure within a few months, although treatment with angiotensin-converting enzyme (ACE) inhibitors such as benazapril can slow the progression of the disease (1,2). Protein-losing nephropathy associated with exposure to *Borrelia burgdorferi* [often called Lyme nephritis or nephropathy (LyN)] is reported in a small proportion of seropositive dogs and also typically progresses rapidly to renal failure (3–6). This case report describes a 6-year-old SCWT that was presented with PLN, marked hypoalbuminemia, and seropositivity for *B. burgdorferi* exposure. Significant improvement of the PLN and serum albumin concentration was only achieved following doxycycline therapy suggesting a diagnosis of Lyme-associated renal disease. The favorable response to effective therapy is contrary to published reports of prognosis for LyN or SCWT-PLN (1–6).

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### Case description

A 6-year-old, spayed female soft-coated wheaten terrier (SCWT) was presented to the Companion Animal Hospital of the Atlantic Veterinary College (AVC) in December of 2008 for investigation of undefined right front leg lameness, generalized peripheral lymphadenomegaly, decreased appetite, and weakness reported to be of 2 to 3 wk duration. The dog had lived in the province of Prince Edward Island (PEI) except for a history of travel to Ontario, Canada, 1 y prior to presentation. Routine vaccinations were up-to-date (rabies, DA2PPC), but the dog had no history of vaccination for Lyme disease. Physical examination showed that the dog had a dull, thin hair coat, pain upon palpation of the right elbow joint, and mild, palpable generalized lymphadenomegaly.

Initial diagnostic work-up included a complete blood (cell) count (CBC), serum biochemistry profile, urinalysis (collected by cystocentesis), thoracic radiographs, radiographs of the right elbow joint, and abdominal ultrasound. The CBC, serum biochemistry, and urinalysis were performed by the AVC Diagnostic Services Laboratory. No abnormalities were detected on CBC. The serum biochemistry showed a mild increase in total protein concentration [72 g/L; reference interval (RI): 56 to 71 g/L], hypoalbuminemia at 18 g/L (RI: 30 to 36 g/L), and a hyperglobulinemia at 54 g/L (RI: 25 to 38 g/L). The urine had a refractometric urine specific gravity (USG) of 1.056, pH 6.5, proteinuria 3+ (Multistix-Bayer Corporation, Elkhart,

**Table 1.** Serum and urine protein data and C6 antibody titers during the monitoring period, 2008 to 2012

| Date | Tot prot g/L | Alb g/L | Glob g/L | A/G | UPC | C6 |
|---|---|---|---|---|---|---|
| 2008 | | | | | | |
| Dec 18[a] | 72 | 18 | 54 | 0.33 | 8.58 | |
| 2009 | | | | | | |
| Jan 6[b] | 78 | 19 | 59 | 0.32 | 3.41 | |
| Feb 3[c] | 74 | 19 | 55 | 0.35 | 5.95 | |
| May 12 | 66 | 26 | 40 | 0.65 | 1.18 | 176 |
| Aug 11[d] | 62 | 31 | 31 | 1.0 | 0.82 | 183 |
| 2010 | | | | | | |
| Jan 28[e] | 61 | 31 | 30 | 1.03 | 0.74 | 75 |
| Aug 17 | 65 | 32 | 33 | 0.97 | 1.17 | |
| 2011 | | | | | | |
| Mar 3 | 56 | 29 | 27 | 1.07 | 1.73 | 41 |
| Jun 23 | 62 | 32 | 30 | 1.07 | 1.95 | 48 |
| 2012 | | | | | | |
| May 20 | 58 | 28 | 30 | 0.93 | 1.84 | |
| Reference interval (RI) | 56–71 | 30–36 | 25–38 | 0.7–1.5 | < 0.50 | < 30 |

Tot prot — total serum protein, alb — serum albumin, glob — serum globulin, A/G — albumin globulin ratio, UPC — Urine protein:urine creatinine ratio, C6 — C6 antibody titer.
[a] Benazapril started.
[b] ASA, Omega-3 diet added.
[c] SNAP *B. burgdorferi* positive, started doxycycline Mar 27 (4 weeks).
[d] ASA discontinued.
[e] Benazapril discontinued (all treatments discontinued).

USA), and 1 to 3 fine granular and hyaline urine casts per low power field (LPF — 200×). One to 3 transitional cells per high power field (HPF — 400×) were visualized, but no significant number of WBCs (0–1/HPF) or RBCs (0/HPF) were present. Urine protein-to-urine creatinine ratio (UPC) was increased at 8.58 [reference limit (RL): < 0.5]. Radiographs were evaluated and abdominal ultrasound was performed by a board-certified radiologist. The radiographs of the thorax and right elbow were unremarkable. Abdominal ultrasound showed a mild medial iliac and mesenteric lymphadenomegaly. Fine-needle aspirates (FNA) of the left prescapular, right prescapular, and right popliteal lymph nodes were evaluated by a board-certified clinical pathologist and demonstrated a benign reactive hyperplasia. A possible breed-related PLN was suspected although other infectious or immune causes of PLN were considered. Treatment with benazepril (Novartis Canada, Mississauga, Ontario) was started at 0.35 mg/kg body weight (BW), PO, q24h. An average systolic blood pressure of 123 mmHg [RL: 150 mmHg (7)] was measured by Doppler prior to the start of Benazepril.

The dog returned periodically over the next 2 mo for re-evaluation. Levels of serum and urine protein over the monitoring period are presented in Table 1. At 2 wk, the lameness and the lymphadenomegaly had resolved and the UPC was improved at 3.41 (RL: < 0.5) although serum albumin (19 g/L) and globulin (59 g/L) concentrations had not improved. Aerobic urine culture (collected by cystocentesis) was negative. The dog was started on aspirin (compounded, AVC pharmacy) 0.5 mg/kg BW, PO, q24h. Commercial renal diet and omega-3 fatty acid supplementation were recommended and the owners complied. One month later, the serum albumin and globulin concentrations were unchanged and the UPC (5.95) showed no further improvement. Average systolic blood pressure was 200 mmHg measured by Doppler; however, the patient was uncooperative and anxious; therefore, true systolic blood pressure could not be determined at this time. The dose of Benazepril was increased to 0.5 mg/kg BW, the other medications were continued and serological evaluation for vector-borne diseases was recommended in light of the combined history of lameness and current proteinuria, although exposure to tick-borne infectious agents was not considered common in PEI at that time. A serum ELISA test for vector-borne agents (SNAP 4Dx; IDEXX Laboratories, Westbrook, Maine, USA.) was positive for *Borrelia burgdorferi* and negative for *Anaplasma phagocytophilum/platys, Ehrlichia canis/chaffeensis,* and *Dirofilaria immitis.* A serum sample was collected for immunofluorescent antibody (IFA) and Western blot (WB) evaluation for exposure to *B. burgdorferi* (Diagnostic Center for Population and Animal Health, Michigan State University, Lansing, Michigan, USA). The IFA was positive for antibodies to *Borrelia burgdorferi* at > 20 480 (RL: < 40) and the WB demonstrated no evidence of antibody response to vaccination for Lyme disease. After repeat questioning, 1 of the owners remembered that a tick was removed from the dog 6 mo prior to the presentation to the AVC. The owner removed the tick himself and never had the tick analyzed. Doxycycline (Apotex, Toronto, Ontario) 5 mg/kg BW, PO, q12h for 4 wk was added to the therapy.

In May of 2009 (5 mo following initial presentation and 2 mo following initiation of doxycycline treatment), the dog was presented for re-evaluation. Serum biochemistry findings showed improvement in serum albumin and globulin concentrations (26 g/L and 40 g/L, respectively) but these values were still outside the RIs. Complete blood (cell) count was within the RI; the UPC was 1.18 (RL: < 0.5) and aerobic urine culture was again negative. Average systolic blood pressure measured by Doppler was 170 mmHg, which was considered to have been influenced by patient anxiety. A serum sample was submitted for quantitative anti-C6 antibody ("C6 quant") determination to obtain a numerical measurement of antibodies to *B. burgdorferi,* and the resulting titer was 176 U/mL (RL: < 30 U/mL) (Vita tech — IDEXX Laboratories, Toronto, Ontario) (see Table 1). The serum was also submitted for IFA for tick-borne diseases; the *B. burgdorferi* titer remained high (> 20 480), and the sample was negative for *A. phagocytophilum* (< 80), *Babesia canis* (< 40), *Ehrlichia canis* (< 40), and *Rickettsia rickettsii* (< 40) (Diagnostic Center for Population and Animal Health, Michigan State University). The dog was improved clinically, with improved hair coat, activity level, and appetite.

In August of 2009, (8 mo after initial presentation to the AVC and 5 mo following initiation of doxycycline treatment), the serum biochemistry and CBC were within RI. The UPC had decreased to 0.82 (RL: < 0.5) and anti-C6 antibody concentration was 183 U/ml (RL: < 30 U/mL, Vita tech — IDEXX Laboratories, Toronto, Ontario). The treatment with Benazepril was decreased to 0.18 mg/kg BW, q24h and aspirin was discontinued.

Thirteen months after initial presentation (10 mo following the start of doxycycline treatment) the dog was clinically normal. Serum biochemistry and CBC were within RI. Anti-C6 antibody concentration and UPC were 75 U/mL (RL: < 30 U/mL) and 0.74 (RL: < 0.5), respectively. Benazepril was discontinued at that time. The UPCs measured 1 and 3 mo after discontinuing all treatment were 0.86 and 0.98, respectively. In August of 2010, 20 mo after the initial presentation, and 7 mo after discontinuation of all therapy, the dog remained clinically normal, serum biochemistry had no abnormalities and UPC was 1.17. This patient has been monitored over the 33 mo since the initial presentation (20 mo after discontinuing all medications), and has had no significant CBC and serum biochemistry alterations while UPC remains < 2.0 (1.73, 1.95, and 1.47 at 27, 30 and 33 mo, respectively). The anti-C6 antibody concentrations were 41 and 48 U/mL (RI: < 30) at 27 and 30 mo, respectively.

## Discussion

The presence of proteinuria and hypoalbuminemia without hypoglobulinemia, in association with a negative urine culture and without concurrent liver dysfunction or gastrointestinal disease is consistent with PLN (1). Urine protein:urine creatinine ratios > 2 are most compatible with glomerular disease (8,9). The lack of significant blood or WBCs in the urine is also supportive of glomerular protein loss. Familial PLN in SCWT is reported to have a prevalence of up to 10%, a female predisposition, and an average age of diagnosis of 6.3 (± 2) years of age (1). Protein losing nephropathy of SCWT is thought to be the result of an immune-mediated disorder resulting in immune complex glomerulonephritis (GN) and typically presents with proteinuria, hypoalbuminemia, and hypercholesterolemia. Rapid progression to renal failure and death with a median survival time of only a few months is typical of SCWT-PLN (1,2). Dysfunction of the immune response in this breed is also suggested by a predisposition to sensitivity to food antigens resulting in protein losing enteropathy (PLE), which can occur separately or concurrently with PLN (1,2).

*Borrelia burgdorferi,* the causative agent of Lyme disease, is carried by the *Ixodes scapularis* tick in the northeastern seaboard of the US and Atlantic Canada (10). Adult *I. scapularis* ticks are found in Prince Edward Island where the ticks are thought to be transported to the island by migratory birds as an endemic tick population has never been identified (10). The submission records of the AVC Diagnostic Services laboratory reveal that 9 of 77 (11.7%) *I. scapularis* ticks submitted from PEI in 2008 were positive for *B. burgdorferi* by PCR (National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, Manitoba) and 19/116 (16.4%) were *B. burgdorferi* positive in 2009 (B. Horney, unpublished data). A number of sera from PEI dogs submitted to AVC laboratory in 2007, 2008, and 2010 for biochemical or endocrine testing (routine or disease investigation) were selected as a convenience sample over several months to obtain information on positivity for *B. burgdorferi* antibodies in the dogs in the province. Results indicated that 2/60 (3.3%), 1/27 (3.7%), and 7/137 (5.1%) were positive for *B. burgdorferi* C6 antibodies (4Dx test), in 2007, 2008, and 2010, respectively (B Horney, unpublished data). In other Canadian provinces, the prevalence of seroconversion to *B. burgdorferi* in dogs is reported to be highest in parts of Ontario 38/1349 (2.8%) and Nova Scotia 15/697 (2.2%) (10). In the northeast United States, the percent of dogs with positive titers for *B. burgdorferi* has been reported to be between 7% and 20%, with some local areas greatly exceeding that proportion (11).

Most seropositive dogs (95%) do not develop clinical disease despite exposure to *B. burgdorferi,* but a syndrome of fever and arthritis has been found to occur in a small proportion of dogs after exposure to *B. burgdorferi* both naturally and experimentally (3). A second, less common syndrome (LyN), characterized by persistent proteinuria, immune-mediated membranoproliferative glomerulonephritis, and typically fatal renal failure has also been associated with *B. burgdorferi* exposure (3–6). This syndrome has a reported breed predilection for golden and Labrador retrievers and Shetland sheepdogs (3,6). Intact *B. burgdorferi* organisms have only rarely been found in the kidney tissue of dogs with presumptive LyN, leading to the conclusion that immune complex formation and glomerular deposition with damage is the most likely pathogenesis for this condition (12,13). There are reports of membranous glomerulonephritis secondary to *B. burgdorferi* infection in humans (14,15).

The combined clinical problems of lameness and PLN of glomerular origin in this SCWT patient, in addition to a history of tick exposure and a positive result for antibodies to *B. burgdorferi,* support a diagnosis of LyN, although SCWT-PLN was considered the top differential on initial presentation. The evidence of significant urine concentrating ability (USG = 1.056) and the absence of azotemia in this patient indicate that renal tubular function and glomerular filtration rate (respectively) were not measurably affected. The concurrent hyperglobulinemia in this patient could be consistent with a selective protein loss (albumin loss exceeds globulins) and/or a reactive protein production (acute phase proteins or immunoglobulins). The lameness and lymphadenomegaly resolved spontaneously, which is typical for Lyme-associated arthritis (3,16). A positive response of the glomerular disorder to antibiotic therapy, as indicated by the decreased serum globulin concentrations, increased albumin concentrations and decreased UPC, lends further support to an infectious cause for the PLN and likely LyN. The UPC did show some improvement following therapy with Benazepril alone, which is likely due to lowered efferent arteriolar resistance and glomerular pressure leading to reduced protein transit across the glomerular filtration barrier. The UPC was still significantly increased at that time and the response seen is similar to the level of improvement reported in proteinuric dogs treated with ACE inhibitors (17). However, the UPC approached the RL only after antibiotic administration. The serum albumin increased only after doxycycline therapy and was within RI 6 mo later, remaining essentially stable over the 2-year monitoring period.

It is impossible to prove that the PLN in this case is LyN. Glomerular damage associated with other infectious agents sensitive to doxycycline therapy could have shown a similar response to therapy. Serum titers to *Leptospira* spp. were not evaluated in this case because the proteinuria associated with canine leptospirosis is typically less severe, especially in the

absence of azotemia, and is unlikely to result in PLN because *Leptospira* spp. infection is associated with an interstitial nephritis not a primary glomerular disorder (18). Other tick-borne agents may infect dogs that have been exposed to *B. burgdorferi,* but the serologic evaluation in this case did not provide any evidence of exposure to *A. phagocytophilum/platys, E. canis/chaffeensis,* or *D. immitis* and blood smear examination provided no evidence of anemia or intraerythrocytic organisms such as *Babesia* spp. Infection with *Bartonella* spp., which was not evaluated in this patient, or other tick-borne agents cannot be completely ruled out.

Tetracyclines have antiprotease and anti-inflammatory effects and administration may result in clinical improvement even in the absence of infectious disease (19). One case report of human glomerulonephritis showed improved UPC during doxycycline treatment but proteinuria increased to pretreatment levels after doxycycline was discontinued (20). Renal biopsy with histologic, electron microscopic, and immunohistochemical evaluation could have supplied further support for immune complex related glomerular damage in this case but would not have been expected to have identified a specific infectious etiology.

Soft-coated wheaten terriers are believed to have a genetic predisposition to disordered immune response (1) and we propose that this predisposition may increase the potential for development of higher levels of circulating immune complexes and subsequent nephropathy after exposure to *B. burgdorferi.* In this scenario "Lyme nephritis" could be an expression of SCWT-PLN in which the inciting antigens triggering the immune complex formation are *B. burgdorferi* antigens. A predisposition to immume-mediated glomerular damage has also been linked to *B. Burgdorferi*-associated GN in humans (15). Identification of PLN and initiation of antibiotic treatment for the presumed inciting *B. burgdorferi* agent, prior to the development of azotemia, irreparable or self perpetuating renal damage and renal failure, could have increased the probability of successful treatment response in this SCWT.

Evaluation of anti-C6 antibody levels in dogs and humans is recommended to identify infection/exposure to *B. burgdorferi* and to differentiate between natural infection and vaccination antibody response because anti-C6 is not incited by vaccine strains of *B. burgdorferi* (3,4). Anti-C6 antibody concentrations were increased and remained stable for over 1 y in dogs, and up to several years in monkeys experimentally infected (without clinical signs) with *B. burgdorferi* and declined within 25 wk following antibiotic treatment for *B. burgdorferi* (16,21). Quantitative anti-C6 antibody evaluation prior to and 4 to 6 mo following antibiotic treatment has been proposed as a tool for assessing successful treatment for *B. burgdorferi* (3,5,21). Unfortunately, in this SCWT the quantitative anti-C6 antibody concentration was not measured until 2 mo following antibiotic therapy. At that time the concentration of 176 U/mL was over 5 times the accepted RL and showed no appreciable difference 3 mo later. The serum anti-C6 antibody concentration decreased over the course of monitoring this patient (75 and 41 U/mL at the 1 and 2 year rechecks, respectively), consistent with decreasing antibody response to *B. burgdorferi,* which has been associated with successful treatment of *B. burgdorferi* (3,5,21). Although natural attenuation of the C6 antibody response over time cannot be completely ruled out, studies in dogs and monkeys have shown this antibody concentration is typically stable over long periods of time (1.5 to 3 y) and does not naturally decline in the absence of antibiotic treatment (16,20). In light of the expected delay between treatment and the decrease in serum C6 antibody levels, the UPC and serum albumin concentrations were better early indicators of response to therapy in this case. The persistence of an anti-C6 antibody concentration level $>$ 30 U/mL and a mildly increased UPC more than 2 y following the initial presentation may indicate persistent renal damage (resulting from or unrelated to the suspected immune complex glomerular damage) and/or low level persistent infection with *B. burgdorferi,* which has been postulated to occur despite antibiotic treatment (3,22,23). There is also some indication that prolonged doxycycline therapy (6 wk or more) may be required in treatment of LyN, although this is controversial (3). Continued monitoring of the serum albumin, UPC, and anti-C6 antibody concentrations is recommended to identify significant or progressive alterations which may warrant additional therapeutic intervention. CVJ

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